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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
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| 10/734,949 | 12/13/2003 | Rosa Maria Rodriguez Sarmiento | 21247 US | 1463 |

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HOFFMANN-LA ROCHE INC.
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| EXAMINER | |
|---|---|
| TRUONG, TAMTHOM NGO | |
| ART UNIT | PAPER NUMBER |
| 1624 | |

DATE MAILED: 09/23/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 10/734,949 | RODRIGUEZ SARMIENTO ET AL. | |
| | Examiner | Art Unit | |
| | Tamthom N. Truong | 1624 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) 1-37 is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) 1-3,5,7,8,11,16,18,22-24,26 and 33-37 is/are rejected.

7)☒ Claim(s) 4,6,9,10,12-15,17,19-21 and 27-32 is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date 3/17 + 5/14/04.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

## DETAILED ACTION

Claims 1-37 are pending.

### *Claim Rejections - 35 USC § 112*

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

1. **Enablement:** Claims 35-37 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The following factors have been considered in the determination of an enabling disclosure:

(1) The breadth of the claims;

(2) The amount of direction or guidance presented;

(3) The state of the prior art;

(4) The relative skill of those in the art;

(5) The predictability or unpredictability of the art;

(6) The quantity of experimentation necessary;

[See ***Ex parte Forman***, 230 USPQ 546 (Bd. Pat. App. & Int., 1986); also ***In re Wands***, 858 F. 2d 731, 8 USPQ 2d 1400 (Fed. Cir. 1988)].

**The breadth of the claims:**

Claim 35 recites: "A method of treating Alzheimer's disease...comprising administering...a compound according to claim 1."

Claim 36 recites: "A method of treating senile dementia ...comprising administering...a compound according to claim 1."

Claim 37 recites: "A method of treating Parkinson's disease...comprising administering...a compound according to claim 1."

Although the three claims are drawn to the treatment of specific diseases, the Markush group in claim 1 encompasses a fairly large number of compounds. Thus, based on the compound's scope, the claimed methods have unduly broad scope.

**The amount of direction or guidance presented:** The specification only describes the *in-vitro* bioassay for determining the inhibition of MAO-B. It does not indicate which compounds have been tested, and only discloses the inhibitory activity in general term of "10 $\mu$M or less, typically of 1 $\mu$M or less, and ideally 0.3 $\mu$M or less." There is no *in-vivo* data on memory improvement for the treatment of Alzheimer's disease or senile dementia. Likewise, there is no *in-vivo* data on motion improvement for the treatment of Parkinson's disease. Furthermore, the specification indicates a dosage range of 0.01-20 mg/kg/day, which is too broad a range for a meaningful effective dosage. Thus, the specification does not provide sufficient

enablement to guide the skilled clinician to select a compound of formula I for the treatment of Alzheimer's disease, senile dementia, or Parkinson's disease.

**The state of the prior art:** Currently in the practice of medicine, Alzheimer's and Parkinson's diseases do not share the same etiology, or manifestation. Alzheimer's disease relates to the availability of acetylcholine while Parkinson's disease relates to the availability of dopamine. While the inhibition of MAO could increase the availability of acetylcholine, and theoretically treat Alzheimer's disease or senile dementia in the early stage, such an inhibition would not be useful once neurons get degenerated.

Furthermore, as evident by the teaching of **Sekiya et. al.** (US 4,668,682), related quinazolone compounds are known for calcium antagonistic, vasodilative, and antihypertensive activities. Also, the teaching of **Houghten et. al.** (US 5,783,577) associates quinzolinone compounds with hypnotic, sedative, analgesic, anticonvulsant, antitussive and anti-inflammatory effects. Note, the hypnotic sedative effects would be contraindicated in the treatment of Alzheimer's disease or senile dementia.

**The relative skill of those in the art:** Even with the advanced training, the skilled clinician would have to engage in undue experimentation to establish data that would adequately support the use of the claimed compounds in the treatment of Alzheimer's diseases, senile dementia or Parkinson's disease, etc. Such a task would require a tremendous amount of effort, time and resources.

**The predictability or unpredictability of the art & The quantity of experimentation necessary:** The pharmaceutical art has been known for its unpredictability due to various

conflicting pathways, or biological factors that are sometimes genetically unique to individuals. In the instant case, the specification only describes bioassay procedure without providing any actual *in-vitro* data. The guidance provided is much too generic, and the state of the art does not support the claimed methods either. Thus, with such a limited teaching, the skilled clinician would have to carry out undue experimentation to use the claimed compounds in the methods recited in claims 35-37.

***Claim Rejections - 35 USC § 103***

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

2. Claims 1-3, 5, 7, 8, 11, 16, 18, 22-24, 26, 33 and 34 are rejected under 35 U.S.C. 103(a) as being unpatentable over **Sekiya et. al.** (US 4,668,682).

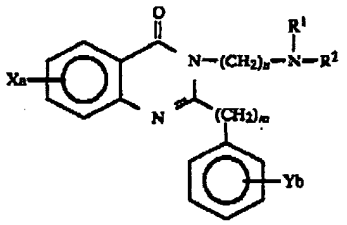
On columns 13 and 14, Table 2 discloses compound #88 (see attached page for structure) which is analogous to a compound of the instantly claimed formula I with the following substituents:

i. $R^1$ is $-(CH_2)_n-NR^5R^6$; wherein both $R^5$ and $R^6$ are alkyl groups;

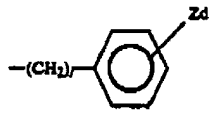
ii. $R^2$ is hydrogen; n = 1;

iii. $R^3$ is benzyl – note because the limitation of "benzyl" is opened to both unsubstituted and substituted.

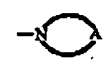
The disclosed compound differs from the claimed compound by having an unsubstituted "phenoxy" group at the 6th position of the quinazolinone ring whereas the instant Formula I requires at least one $R^4$ on the "benzyloxy" at the 7th position of the quinazolinone ring. However, such a difference can be remedied by the generic teaching of formula I on columns 2-4 – also see the excerpt on the right hand side.



wherein, X represents a hydrogen atom, an alkyl group having 1 to 5 carbon atoms, an alkoxy group having 1 to 5 carbon atoms, a phenoxy group, a benzyloxy group, a halogen atom or a hydroxy group; Y represents an alkyl group having 1 to 5 carbon atoms, an alkoxy group having 1 to 5 carbon atoms, a benzyloxy group, a halogen atom or a nitro group; $R^1$ represents a hydrogen atom or an alkyl group having 1 to 5 carbon atoms; $R^2$ represents an alkyl group having 1 to 5 carbon atoms or a group of Formula (2)

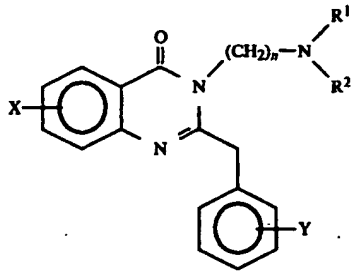


[wherein, Z represents a hydrogen atom, an alkyl group having 1 to 5 carbon atoms, an alkoxy group having 1 to 5 carbon atoms or a halogen atom; d is an integer of 1 to 3; and l is an integer of 1 to 5]; or $R^1$ and $R^2$ represent together with the nitrogen atom to which they are attached, a cyclic amino group of the formula:



[wherein, A represents an alkylene group having 2 to 6 carbon atoms or a group of the formula $-(CH_2)_2-O-(CH_2)_2-$]; a and b are independently an integer of 1 to 3; and n and m are independently an integer of 1 to 5, or a pharmaceutically acceptable acid addition salt thereof, a process for preparing said compound, a composition comprising said compound as an active ingredient and a method of treatment by use of said compound. The compounds of the present invention have calcium antagonistic, vasodilative, and antihypertensive activities.

TABLE 2-continued



| Example No. | Compound No. | X | Y | $R^1$ / $R^2$ | n | Discrimination between free base and salt | Yield (%) | Melting point (°C.) | Mass spectrum (m/e) M+ | Mass spectrum (m/e) Base peak ion |
|---|---|---|---|---|---|---|---|---|---|---|
| 76 | 76 | " | " | " | 3 | free base | 43 | oily | 495 | 86 |
| 77 | 77 | 6,7-dimethoxy | " | dimethylamino | 2 | " | 64 | " | 427 | 58 |
| 78 | 78 | " | 4-methoxy | " | 2 | " | 73 | " | 397 | 58 |
| 79 | 79 | 6-methoxy-7-isopropoxy | 2,5-dimethoxy | " | 2 | " | 62 | " | 455 | 58 |
| 80 | 80 | 6-methoxy-7-isopropoxy | 4-methoxy | " | 2 | " | 45 | " | 425 | 58 |
| 81 | 81 | 6-isopropoxy-7-methoxy | 2,5-dimethoxy | " | 2 | " | 77 | 115–118 | 455 | 58 |
| 82 | 82 | 6-isopropoxy-7-methoxy | 4-methoxy | " | 2 | hydrochloride | 58 | 235–239 | 425 | 58 |
| 83 | 83 | 6-isopropoxy-7-methoxy | " | methylamino | 2 | free base | 28 | oily | 411 | 355 |
| 84 | 84 | 6-ethoxy-7-methoxy | " | dimethylamino | 2 | " | 77 | " | 411 | 58 |
| 85 | 85 | 6-ethoxy-7-methoxy | " | " | 3 | " | 77 | " | 425 | 58 |
| 86 | 86 | 6-isopropoxy | 2-methoxy | " | 2 | hydrochloride | 70 | 178–183 | 395 | 58 |
| 87 | 87 | 6-isopropoxy-7-methoxy | " | " | 2 | " | 97 | 200–203 | 425 | 58 |
| 88 | 88 | 6-phenoxy | 2,5-dimethoxy | " | 2 | " | 49 | 184–187 | 459 | 58 |

### Synthesis example 3

2-(2-Methoxyphenylmethyl)-4H-3,1-benzoxazin-4-one

Following the same procedure as in Synthesis example 2, 2-(2-methoxyphenylmethyl)-4H-3,1-benzoxazin-4-one was obtained from anthranilic acid and 2-(methoxyphenylacetic acid chloride as starting materials via 2-(2-methoxyphenylmethylcarbonyl amino)benzoic acid as an intermediate (yield: 60%).

m.p. 102°–104° C.

Mass spectrum (m/e): 267 ($M^+$), 146 (Base peak ion)

Infrared absorption spectrum ($cm^{-1}$): 1740, 1635, 1595

### EXAMPLE 89

2-(2-Methoxyphenylmethyl)-3-[2-{N-(3,4-dimethoxyphenylethyl)-N-methylamino}ethyl]-4(3H)-quinazolinone hydrochloride (Compound No. 89; Synthesis process B)

268 mg (1 mmol) of 2-(2-methoxyphenylmethyl)-4H-3,1-benzoxazine-4-one and 238 mg (1 mmol) of 2-[[N-[2-(3,4-dimethoxyphenyl)ethyl]-N-methylamino]]ethylamine were heated in xylene (10 ml) under reflux for 10 hours . After the xylene was distilled off, the residue obtained was purified by silica gel column chromatography (eluent; 2% ethanol/chloroform) to obtain 107 mg (52%) of 2-(2-methoxyphenylmethyl)-3-[2-{N-(3,4-dimethoxyphenylethyl)-N-methylamino}ethyl]-4(3H)-quinazolinone as an oily substance. Subsequently, the thus obtained quinazolinone was dissolved in ethanol (2 ml) and to the resulting soluion there was added a 7% hydrogen chloride-ethanol solution (1 ml). Further, ether was added to the reaction mixture thus obtained, and the precipitated colorless crystals were collected by filtration to obtain 99 mg of the hydrochloride which is the desired compound.

m.p.: 171°–175° C. (decomposition)

Mass spectrum (m/e): 487 ($M^+$), 293 (Base peak ion)

Analysis Calculated for $C_{29}H_{33}N_3O_4.HCl$: C, 66.46; H, 6.54; N, 8.02%;

Found: C, 66.23; H, 6.75; N, 7.89%.

### EXAMPLES 90 to 132

2-(Substituted phenylmethyl)-3-[N-alkyl-N-(substituted phenylalkyl)aminoalkyl]-4(3H)-quinazolinone derivatives (Compound Nos. 90 to 132)

The captioned .compounds were synthsized in the same manner as in Example 89 except that the 2-(2-methoxyphenylmethyl)-4H-3,1-benzoxazin-4-one was replaced by the corresponding 4H-3,1-benzoxazin-4-one derivatives, and the 2-[N-{2-(3,4-dimethoxyphenyl)ethyl}-N-methylamino]ethylamine was replaced by the corresponding N-alkyl-N-(substituted phenylalkyl)aminoalkylamines. The results obtained are shown in Table 3.

The disclosed variable X can be at $6^{th}$ or $7^{th}$ position on the quinazolinone ring, and it can represents a "phenoxy" group as well as a "benzyloxy" group. Thus, there is an equivalent teaching for X as "phenoxy" and "benzyloxy" at either the $6^{th}$ or $7^{th}$ position. As for the substitution on such a group, column 4 of US'682 indicates that X can also be substituted (see lines 10-15). Possible substituents on X can be seen in compounds #106 and 107 in Table 3 on columns 15-16 (see attached page).

The "Synthesis process E" of US'682 corresponds to the process recited in the instant claim 34. The disclosed formula 7 corresponds to the instant formula IV with $R^3$ as a "benzyl" group. Likewise, the disclosed formula (10) corresponds to the instant formula (V) with $R^1$ as "-$(CH_2)_n$-$NR^5R^6$".

The disclosed compounds have calcium antagonistic, vasodilative, and antihypertensive activities. Thus, with the equivalent teaching provided, the skilled medicinal chemist would have been motivated to select some compounds of the instantly claimed formula I because those compounds would have been expected to have the same pharmacological activities disclosed in US'682.

Therefore, at the time that the invention was made, it would have been obvious to make and use some compounds of formula (I) in view of the teaching above.

***Claim Objections***

3. Claims 4, 6, 9, 10, 12-15, 17, 19-21 and 27-32 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the

limitations of the base claim and any intervening claims. The compounds recited in these claims either have $R^1$ as a group that is not mono- (or di)-alkylamino-$(CH_2)_n$, or $R^3$ is not a "benzyl" group. The teaching of Sekiya et. al. does not teach or fully suggest such a compound.

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Any inquiry concerning this communication or earlier communications from the examiner should be directed to Tamthom N. Truong whose telephone number is 571-272-0676. The examiner can normally be reached on M-F (9:30-6:00).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James O. Wilson can be reached on 571-272-0661. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

***Tamthom N. Truong***
***Examiner***
***Art Unit 1624***

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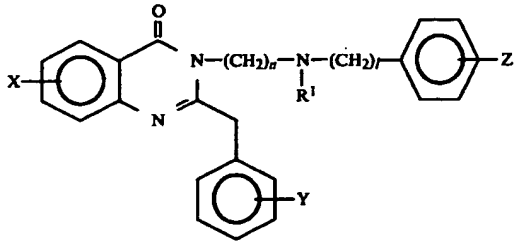
9-13-05

JAMES O. WILSON
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600

TABLE 3




| No. | No. | X | Y | $R^1$ | Z | n | l | Discrimination between free base and salt | Yield (%) | Melting point (°C.) | Mass spectrum (m/e) $M^+$ | Mass spectrum (m/e) Base peak ion |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 90 | 90 | hydrogen atom | 2-methoxy | methyl | hydrogen atom | 2 | 2 | hydrochloride | 51 | 180–210 | 427 | 293 |
| 91 | 91 | " | " | " | " | 2 | 1 | " | 50 | 175–185 | 413 | 134 |
| 92 | 92 | " | " | " | " | 3 | 2 | free base | 57 | oily | 441 | 307 |
| 93 | 93 | " | 2,5-dimethoxy | " | 3,4-dimethoxy | 2 | 2 | " | 23 | " | — | 337 |
| 94 | 94 | " | 4-chloro | " | hydrogen atom | 2 | 2 | hydrochloride | 42 | 180–190 | 431 | 297 |
| 95 | 95 | " | 2-methyl | " | " | 2 | 2 | free base | 53 | oily | 411 | 277 |
| 96 | 96 | " | 3-methyl | " | " | 2 | 2 | " | 45 | " | 411 | 277 |
| 97 | 97 | " | 2-isoproxy | " | " | 2 | 2 | " | 43 | " | 455 | 321 |
| 98 | 98 | " | 2-methoxy | " | " | 2 | 3 | " | 75 | " | 441 | 293 |
| 99 | 99 | " | " | " | " | 2 | 4 | hydrochloride | 44 | 132–140 | 455 | 176 |
| 100 | 100 | " | " | ethyl | " | 2 | 2 | free base | 72 | oily | 441 | 162 |
| 101 | 101 | " | " | buthyl | " | 2 | 2 | " | 19 | " | 469 | 293 |
| 102 | 102 | 6-isopropoxy | 2,5-dimethoxy | methyl | 3,4-dimethoxy | 2 | 2 | " | 14 | " | 575 | 381 |
| 103 | 103 | " | " | " | " | 3 | 2 | " | 11 | " | 589 | 395 |
| 104 | 104 | " | " | " | hydrogen atom | 3 | 2 | " | 9 | " | 529 | 395 |
| 105 | 105 | 6-sec-butoxy | " | " | 3,4-dimethoxy | 2 | 2 | " | 29 | " | — | 265 |
| 106 | 106 | 6-(4-chloro-phenoxy) | " | " | " | 2 | 2 | hydrochloride | 36 | 106–111 | 643 | 449 |
| 107 | 107 | 6-(4-methoxy-phenoxy) | " | " | " | 2 | 2 | " | 23 | 100–106 | 639 | 445 |
| 108 | 108 | hydrogen atom | " | " | " | 3 | 2 | free base | 37 | oily | 531 | 265 |
| 109 | 109 | 6-n-butoxy | " | " | " | 2 | 2 | " | 33 | " | 589 | 395 |
| 110 | 110 | 6-n-pentoxy | " | " | " | 2 | 2 | " | 29 | " | 603 | 409 |
| 111 | 111 | 6-isopentoxy | " | " | " | 2 | 2 | " | 26 | " | 603 | 409 |
| 112 | 112 | hydrogen atom | 4-methoxy | " | " | 2 | 2 | " | 31 | " | 487 | 293 |
| 113 | 113 | " | 2-chloro | " | " | 2 | 2 | " | 17 | " | — | 297 |
| 114 | 114 | 6-methyl | 2,5-dimethoxy | " | " | 2 | 2 | " | 21 | " | 531 | 337 |
| 115 | 115 | hydrogen atom | 3,4-dimethoxy | " | " | 2 | 2 | " | 43 | " | 517 | 323 |
| 116 | 116 | 6-iodo | 2,5-dimethoxy | " | " | 2 | 2 | " | 56 | " | 643 | 449 |
| 117 | 117 | 6-isopropoxy | 2-methoxy | " | " | 2 | 2 | " | 37 | " | 545 | 351 |
| 118 | 118 | " | 4-methoxy | " | " | 2 | 2 | " | 37 | " | 545 | 351 |
| 119 | 119 | " | 2-chloro | " | " | 2 | 2 | " | 40 | " | 549 | 355 |
| 120 | 120 | " | 3,4-dimethoxy | " | " | 2 | 2 | " | 51 | " | 575 | 381 |
| 121 | 121 | 6-ethoxy | 2,5-dimethoxy | " | " | 2 | 2 | " | 22 | " | 561 | 367 |
| 122 | 122 | 6-methoxy | " | " | " | 2 | 2 | " | 51 | " | 547 | 353 |
| 123 | 123 | hydrogen atom | " | " | 3-methoxy | 2 | 2 | " | 14 | " | 487 | 323 |
| 124 | 124 | 6-isopropoxy | " | " | " | 2 | 2 | " | 13 | " | 545 | 381 |
| 125 | 125 | hydrogen atom | " | " | 4-methyl | 2 | 2 | " | 22 | " | 471 | 323 |
| 126 | 126 | 6-isopropoxy | " | " | " | 2 | 2 | " | 18 | " | 529 | 381 |
| 127 | 127 | " | " | " | 4-methoxy | 2 | 2 | " | 28 | " | 545 | 381 |
| 128 | 128 | hydrogen atom | " | " | 4-chloro | 2 | 2 | " | 20 | " | 491 | 323 |
| 129 | 129 | 6-isopropoxy | " | " | " | 2 | 2 | " | 9 | " | 549 | 381 |
| 130 | 130 | hydrogen atom | " | " | 2,5-dimethoxy | 2 | 2 | " | 26 | " | 517 | 323 |
| 131 | 131 | 6-isopropoxy | " | " | " | 2 | 2 | " | 17 | " | 575 | 381 |
| 132 | 132 | hydrogen atom | " | " | 4-methoxy | 2 | 2 | " | 48 | " | 487 | 323 |

Synthesis example 4

2-(2,5-Dimethoxyphenylacetylamino)-5-methyl-N-(2-dimethylaminoethyl)benzamide

0.50 g (1.5 mmol) of 2-(2,5-dimethoxyphenylacetylamino)-5-methylbenzoic acid (m.p. 163 to 164.5° C.) synthesized in the same manner as in Synthesis example 1 for 2-(2,5-dimethoxyphenylacetylamino)-5-isopropoxybenzoic acid was suspended in dichloromethane (10 ml), and then to the resulting mixture was added dropwise a dichloromethane solution containing 0.33 (1.6 mmol) of dicyclohexylcarbodiimide (DCC) under ice cooling. Subsequently, 0.14 g (16 mmol) of 2-dimethylaminoethylamine was added dropwise thereto and the mixture thus obtained was stirred for 2 hours at room temperature. The precipitates were filtered off and the mother liquid was concentrated by distillation. The thus obtained residue was purified by silica gel column chromatography (eluent; dichloromethane:ethanol=97:3) to obtain 0.41 g (yield 68%) of 2-(2,5-dimethoxyphenylacetyamino)-5-methyl-N-(2-dimethylaminoethyl)benzamide.

m.p. 105°–110° C.